Remarks

Reconsideration of this Application is respectfully requested.

Claims 41, 45-48, 50-54, 58, 64, 65 and 93-97 are pending in the application, with claims 41, 93 and 94 being the independent claims. Claims 42-44, 49, 55-57, 59-63 and 66-92 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 93-97 are sought to be added. Claims 41, 45-48, 51, 54, 58, and 64 are sought to be amended.

Support for the amendment to claim 41 can be found, *inter alia*, on page 196, Table 22 of the specification.

Support for the amendments to claims 45-48 and new claims 93 and 94 can be found, *inter alia*, on page 50, lines 17-32; page 42, lines 26-27, page 43, lines 1-4; page 51, line 30 - page 52, line 11; page 53, lines 33-34; page 46, lines 28-33; page 82, lines 2-3 and page 83, lines 25-29 of the specification.

Support for claims 51 and 54 can be found, *inter alia*, on page 12, lines 3-5 of the specification.

Support for claims 94 - 97 can be found, *inter alia*, on page 55, lines 27-32, page 43, lines 1-10 and page 55, line 33 - page 56, line 15 of the specification.

The amendment to the specification has been made to conform with U.S.P.T.O. requirements. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Oath/Declaration

The Examiner objected to the declaration as it did not contain the current priority claim as amended by Applicants. Applicants submit herewith a new declaration indicating the current priority claim signed by all but one of the inventors. A declaration with all of the inventors was not possible prior to the filing of this amendment and reply. Applicants will forward the declarations of the remaining inventors once they are available.

Objection to the Specification

The Examiner objected to the specification because it contained an embedded hyperlink on page 16 at line 7 of the specification. Applicants have amended the specification so that the hyperlink is no longer in browser-executable code. Applicants believe the objection is now moot.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 49, 54-58, 68, 69, 71 and 75 under 35 U.S.C. § 112, first paragraph for allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Paper No. 061004, p. 3). Specifically the Examiner stated that "one of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a

representative number of species to described the genus as broadly claimed." (*Id.*) Applicants respectfully traverse.

The test for the written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit has re-emphasized the well-settled principle of law that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,'" *Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000). Furthermore, an Applicant is not required to explicitly describe the subject matter. *Unocal*, 208 F.3d at 1000; *see also* M.P.E.P. § 2163.02 ("The subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.") The Court emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. Indeed, as the court noted, "the issue is whether one of skill in the art could derive the claimed ranges from the patent's disclosure." *Unocal*, 208 F.3d at 1001.

Applicants note that the Federal Circuit stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> A description of a genus of cDNAs may be achieved by means of a recitation of [1] a representative number of cDNAs, defined by nucleotide

> sequence, falling within the scope of the genus or [2] of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus . . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406. Here, the claimed peptides of the present application, and compositions comprising those peptides, share a common structural feature that can satisfactorily support the genus of molecules which contain that common structural feature. Applicants assert that the peptides of the present invention all contain as the common structural feature the peptide of SEQ ID NO:4233. Thus, analogous to the cDNAs discussed above, the presence of the peptide SEQ ID NO:4233 is a structure feature common to all of the peptides of the invention and as such is a feature that constitutes a substantial portion of the genus.

Without acquiescing in the propriety of the rejection, claims 49, 55-57, 69, 69, 71 and 75 have been cancelled. Applicants will argue the rejection as it now may relate to new claims 93-97 and amended claims 45-48 and 51, which all depend from claim 93, as well as amended claims 54 and 58. The Examiner has stated that there is "no disclosure of compositions comprising other peptides that are not Th epitope peptides or TAA CTL epitope peptides, or flanking sequences from the Her-2/neu protein." (Paper No. 061004, p.3). The Examiner has however indicated that the specification discloses "Her-2/neu peptides linked to carriers or linked as homopolymers or heteropolymers, and where different peptide epitopes are used to make up the polymer. . . ."

Amended claim 54 is now directed to a composition comprising a peptide consisting of SEQ ID NO:4233 and "one or more different immunogenic peptides." The peptide of SEQ ID NO:4233 is clearly described in the specification, specifically the

sequence listing. Applicants argue that the composition of claim 54, as amended, does not recite the inclusion of just *any* peptide, but an *immunogenic* peptide, which is described in the application as "a peptide that comprises an allele-specific motif or supermotif such that the peptide will bind an HLA molecule and induce a CTL and/or HTL response." (p. 12, lines 3-5 of the specification). The motifs and supermotifs are described in Tables I - III and pp. 22-30 of the specification. Thus, Applicants argue that "a composition comprising the peptide of claim 41 and one or more different immunogenic peptides" is clearly supported in the specification such that one of skill in the art would have reasonably concluded that the inventor, at the time the application was filed, had possession of the genus as claimed in claims 54 and 58, which depends from 54.

New claim 93 recites "A linked polypeptide comprising a peptide consisting of the sequence KVFGSLAFV (SEQ ID NO:4233) linked to one or more members selected from the group consisting of: (a) a T helper peptide; (b) one or more spacer molecules, (c) a carrier; (d) a lipid; and (e) one or more different immunogenic peptides. Claims 45-48 and 51 have been amended to depend from claim 93, and various linked polypeptides. New claims 94-97 are directed to compositions comprising a linked polypeptide as recited in claim 93. Each of the claims requires the sequence of SEQ ID NO:4233, so one of skill in the art would be easily able to identify members of the genus claimed herein. Each member will contain the sequence of SEQ ID NO:4233. The Examiner has stated that certain additional limitations of claim 93 and 94, as well as the dependent claims, such as a carriers or heteropolymers (different antigenic peptides linked to the peptide of SEQ ID NO:4233) are disclosed in the specification. *See* Paper No. 061004,

p. 3, #6, ¶4. Other limitations such as T helper peptide, spacer molecules and lipids are well known in the art and described in detail in the specification. *See*, for example, p. 50-51. Applicants also note that the Examiner can refer to the table filed with the Preliminary Amendment of September 2, 2003 which references support in the present specification, as well as the priority application, for claim language. Applicants provide an additional copy herewith as Exhibit A for the Examiner's convenience.

Thus, Applicants respectfully assert that one of skill in the art would have reasonably concluded that the inventor, at the time the application was filed, had possession of the genus of molecules as claimed in new claims 93 and 94 as well as dependent claims 45-48 and 51 and 95-96. Therefore, the written description requirement has been fulfilled and Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 49, 54-58, 68, 69, 71 and 75 under 35 U.S.C. § 112, first paragraph for allegedly containing "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention." (Paper No.061004, p. 4). Specifically the Examiner stated that "the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass compositions comprising SEQ ID NO: 4233 or SEQ ID NO: 4239 and *any* other peptide(s) or any other flanking amino acid sequences." (Paper No. 061004, p. 4). Applicants respectfully traverse.

Without acquiescing in the propriety of the rejection, claims 49, 55-57, 69, 69, 71 and 75 have been cancelled. New claims 93 and 94, and their respective dependent claims 45-48, 51 and 95-97, as well as claims 54 and 58 are directed to compositions comprising a peptide consisting of SEQ ID NO:4233; a linked polypeptide comprising the peptide consisting of SEQ ID NO:4233 linked to one or more members selected from the group consisting of: (a) a helper T peptide; (b) one or more spacer molecules; (c) a carrier; (d) a lipid; and (e) one or more different immunogenic peptides; or a composition comprising a linked polypeptide as described above.

In order for a claim to be enabled, the specification must teach one of ordinary skill in the art to make and use the invention without undue experimentation. The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: 1) the guidance provided by the specification; 2) the amount of pertinent literature; 3) the presence of working examples; and 4) the predictability of the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *See id.*

The Examiner points to two references: Shastri *et al.*, *J. Immunol.* 155: 4339-4346 (1995) and Eisenlohr *et al.*, *J. Exp. Med.* 175: 481-487 (1992) to make the argument that presentation of endogenous peptide MHC class I complexes is influenced by C-terminal flanking residues and are precisely cleaved products. (Paper No.061004, p. 4). Applicants assert that the compositions and linked polypeptides of the present invention will retain the functionality of the original molecule. Indeed, the linked

polypeptides of the claimed invention are those that retain the functionality of the peptide of SEQ ID NO:4233 and may even boost or broaden the functionality. One of skill in the art would easily be able to screen for such molecules using assays known in the art and described in the specification. This would not be "undue experimentation" as discussed below.

Enablement is not precluded if some experimentation is required so long as it is not "undue". *In re Wands*, 585 F.2d 731, 737 (Fed. Cir. 1988). In *Wands*, the court held that a specification was enabling for obtaining antibodies needed to practice the invention because it contained considerable guidance, there was a high level of skill in the art, and all methods to needed to practice the invention were well known. Applicants note that obtaining antibodies is not a trivial exercise, but yet it was considered routine. Like in *Wands*, a person of skill in the art for the claimed invention has a doctorate or equivalent and would easily be able to identify whether a given peptide claimed herein would have the requisite binding and/or immunogenicity for desired use. First, binding assays can be performed to screen candidates as described in Example 1. Then successful candidates can be further screened, if necessary, using the methods of Example 3. Further, the specification cites art teaching these methods. Thus, like in *Wands*, the skill in the art is high, the specification provides ample guidance and all methods needed are well known.

The Examiner is also reminded of *Ex parte Mark*, 12 USPQ2d 1905 (BPAI), which stands for the proposition that claims directed to a "biologically active" protein are enabled if, at the time of filing, it would have been routine for the skilled artisan to identify such a protein using a conventional screening assay, which Applicants assert the

methods of Examples 1 and 3 are. Thus, the fact that any *given* candidate polypeptide might not have binding or immunogenic activity does not militate against a conclusion of enablement provided that one skilled in the art could have readily assayed even a large number of candidates to find at least a reasonable number of "winners".

Importantly, Applicants assert that the addition of additional molecules to the peptide does not necessarily affect its binding. Indeed, for the claimed peptide to bind to an HLA, it is first processed inside the cell prior to association with the appropriate HLA. It was known by the earliest claimed priority date that these epitopes are typically processed from larger proteins by intracellular proteosomes that recognize cleavage sites adjacent to the epitope, thus allowing binding of the processed epitope to HLA. Del Val *et al.*, *Cell* 66:1145-1153 (1991) (of record as document AT4); Eisenlohr *et al.*, *J.Exp.Med.* 175:481-487 (1992) (of record as document AS6). Del Val *et al.* produced chimeric proteins containing a known epitope at different positions within an unrelated protein. Del Val *et al.*, abstract. They found that although the yield of processed epitope differed depending on the positioning of the epitope within the chimera; nonetheless, the chimeras *were* correctly processed to produce the epitope. *Id.*, abstract and 1149, col. 2, 3d full paragraph. Eisenlohr *et al.* also showed that flanking residues influence epitope processing. Eisenlohr *et al.*, abstract. They also showed that the "the effect of negatively acting flanking sequences can be overcome by additional flanking sequences." *Id.*, 485, col. 2, 3d paragraph. The results of Del Val *et al.* and Eisenlohr *et al.* were reviewed in Yewdell and Benninck, *Adv. Immunology 52*:1-123 (1992) (of record as document AR24). Yewdell and Benninck summarized other studies in which epitopes were placed in recombinant proteins and were able to be processed no matter where they were

located. Yewdell and Benninck at 31-32. Finally, a multiepitope vaccine involving HIV antigens is in clinical trials, demonstrating that more than one epitope can clearly be used to generate an immune response. *See* Epimmune Inc. website (http://www.epimmune.com/technology/vaccineprograms.cfm).

Therefore, including additional flanking molecules would not necessarily prevent binding of the cleaved peptide (SEQ ID NO:4233) to the HLA peptide binding domain as they will be removed during processing. Clearly, many epitopes capable of retaining their function within the context of a larger peptide or molecule are well known in the art. Further, screening assays for binding are routine as described above.

In view of the above evidence, Applicants assert that the enablement requirement for the claimed invention is amply met by the specification and the state of the art at the time of filing. Therefore, Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 45-48 and 63-68 under 35 U.S.C. § 112, second paragraph as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No.061004, p. 5).

The Examiner has rejected claims 45 and 63 as allegedly being indefinite in the recitation of "The peptide of claim 41, which is fused to a T-helper epitope" as the peptide of claim 41 is 9, 10 or 11 amino acid residues in length. (Paper No.061004, p. 5). Not acquiescing in the propriety of the rejection, claim 45 has been amended to

depend from new claim 93 which is not limited to a peptide which is 9, 10 or 11 amino acids in length. Additionally, claim 63 has been cancelled.

Claim 46 has been rejected by the Examiner as allegedly being indefinite in the recitation of "The peptide of claim 41, which is fused to spacer or linker amino acids" considering that the peptide of claim 41 is 9, 10 or 11 amino acids in length. (Paper No.061004, p. 5). Not acquiescing in the propriety of the rejection, Claim 45 has been amended to depend from new claim 93 which is not limited to a peptide which is 9, 10 or 11 amino acids in length.

Claims 47 and 67 have been rejected by the Examiner as allegedly being indefinite in the recitation of: the peptide of claim 41 or 59, respectively, which is fused to a carrier considering the peptide of claim 41 and 51 is 9, 10 or 11 amino acids in length. (*See* Paper No. 061004, p. 5). Not acquiescing in the propriety of the rejection, claim 47 has been amended to depend from new claim 93 which is not limited to a peptide which is 9, 10 or 11 amino acids in length. Claim 67 has been cancelled.

Finally, the Examiner has rejected claims 48 and 68 for allegedly being indefinite in the recitation of the peptide of claims 48 or 68 respectively, which is liked to a lipid given the length limitation in base claims 41 and 59. (*See* Paper No.061004, p. 5). Not acquiescing in the propriety of the rejection, claim 48 has been amended to depend from new claim 93 which is not limited to a peptide which is 9, 10 or 11 amino acids in length. Claim 68 has been cancelled.

Thus, Applicants believe that all of the rejections have been rendered moot by amendment and as such respectfully request that the Examiner withdraw the rejections.

Rejections under 35 U.S.C. § 103

Claims 41, 44, 54, 58, 59, 62, 72, 74, and 75 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Kawashima *et al.*, *Human Immunology* 59:1-4 (1998) (hereinafter "Kawashima") in view of Sidney *et al.*, *Immunology Today* 17:261-266 (1996) (hereinafter "Sidney) and Rowland-Jones *et al.*, *J. Clinical Invest.* 102:1758-1765 (1998) (hereinafter "Rowland-Jones"). Specifically, the Examiner states that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the Her2[9369] peptide of epitope KIFGSLAFL taught by Kawashima et al by substituting a V at position 2 and a V at position 9." (Paper No.061004, p. 6). Applicants respectfully traverse this rejection.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To accomplish this, the Examiner must provide both a suggestion or motivation to combine the art and a reasonable expectation of obtaining the claimed invention based upon that combination of art. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner can satisfy this burden, in part, by showing some objective teaching in the prior art, or that knowledge generally available to one of ordinary skill in the art, would lead that individual to combine the relevant teachings of the cited art in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). This, the Examiner has not done.

Specifically, the alleged motivation for one of ordinary skill provided by the Examiner was:

> in order to make a peptide that would bind with higher affinity to HLA-A*6802 the allele that is present in high frequency in the black population as taught by Kawashimi et al because Kawashimi et al teach a peptide epitope KIFGSLAFL that binds HLA-A*6802 with low affinity and Sidney et al teach the supermotif for binding to HLA-A2-like alleles (which includes HLA-A*6802) includes a V at position 2 and position 9 and Rowland-Jones et al teaches V at position 2 and 9 for binding to HLA-A*6802.

(Paper No. 061004, p. 6-7). Applicants disagree. As discussed below, one of skill in the art would not have been motivated to choose the single epitope KIFGSLAFL from the 23 Her2/neu peptides discussed in Kawashimi, and further would not have been motivated by Sidney or Rowland Jones to modify any one peptide of Kawashimi in such a way as to arrive at Applicants' specific peptide KVFGSLAFV.

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient to establish a *prima facie* case of obviousness. MPEP § 2144.08 II, citing *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994). The Examiner must determine whether one of skill in the art "would have been motivated to make the claimed invention as a whole, i.e. to select the claimed species or subspecies from the disclosed prior art genus." MPEP § 2144.08.II.A.4. Applicants point out that the Federal Circuit has declined to adopt a per se rule that a disclosure of a chemical genus renders obvious any species that happens to fall within it, irrespective of how broad the genus. *See In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992); *see also In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994).

Obviousness cannot be established by combining or modifying the cited art to produce the claimed invention unless there is some teaching, suggestion or motivation to do so. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to

render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure.") Nowhere has the Examiner provided a reason for one of skill in the art to chose the claimed peptide out of all of the possible choices suggested by the combination of references. Furthermore, the Examiner has provided no reason why one of skill in the art producing peptide antigens from the Her2/neu polypeptide, which is overexpressed in various types of cancer, would have relied upon Rowland-Jones which is directed to human immunodeficiency virus (HIV) and not cancer. Thus, no adequate motivation has been provided to combine the references cited. Applicants assert that the Examiner has failed to make a *prima facie* case of obviousness.

Kawashima discloses a broad genus of Her2/neu peptides and does not single out the specific peptide KIFGSLAFL relied upon by the Examiner as the basis of the obviousness rejection. Even *assuming arguendo* that the Examiner's choice of a single peptide out of the 23 disclosed is Kawashima is proper, there is still no motivation to combine this reference with Sidney or Rowland-Jones. The Examiner relies upon Sidney and Rowland-Jones to provide the motivation for producing a molecule which would bind with higher affinity to the HLA-A*6802 allele as Kawashima teaches that the KIFGSLAFL peptide binds with low affinity to the HLA-A*6802 allele. The Examiner has stated that the peptide of SEQ ID NO:4233 (KVFGSLAFV) is not taught in Kawashima. *See* Paper No. 061004, p. 6.

Sidney does not provide motivation to produce the claimed peptide of SEQ ID NO:4233. The Examiner indicates that Sidney teaches the supermotif for binding to HLA-A2-like alleles is AILMVT at position two of the peptide and AILMVT at the carboxy terminus of the peptide. (*See* Paper No. 061004, p. 6). Given the peptide taught by Kawashima in combination with the teaching of Sidney, the two references suggest a possible 64 peptides which would potentially bind HLA-A2-like MHC alleles[1]. Thus, Sidney does not provide motivation to arrive at the specific peptide of the claimed invention, KVFGSLAFV. The Examiner provides no motivation as to why this specific peptide would be singled out by one of skill in the art. It is merely a single member of a genus of predicted peptides.

Rowland-Jones does not cure the deficiencies of Sidney. The Examiner states that "Rowland-Jones et al teach use of a VT at P2 and VL at P9 motif for predicting peptides that bind to HLA-A*6802." (Paper No. 061004, p. 6). Applicants assert that the Examiner has mischaracterized Rowland-Jones. The section that the Examiner references indicates that the authors of this reference did not know the motif for predicting peptides which would bind to HLA-A*6802. Indeed, the reference states that "[a]lthough the peptide-binding motif ***has not*** been determined for HLA-A*6802, we used information about the B and F pocket residues ***to predict a motif*** identical to that

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[1] K*FGSLAF* = peptide taught by Kawashima with two positions available for any one of the 6 amino acids taught by Sidney (AILMVT at positions 2 or C-terminus). Thus a total of 64 peptides could be possible candidates taught by the two references. 2 positions open, with a possible choice of 6 amino acid for each position = 2^6 = 64 potential peptide candidates.

determined for HLA-A69, namely valine (V) or threonine (T) at P2 and V or Leucine (L) at P9." (Rowland-Jones, p. 1759 at the second full paragraph) (emphasis added). Thus at best, Rowland-Jones speculates on a suitable motif, which is an insufficient basis for one of skill in the art to have concluded that VT at position 2 and VL at position 9 was the suitable binding motif for HLA-A*6802. Thus, Kawashima in combination with Rowland-Jones does not arrive at the claimed invention or disclose all of the limitations of Applicants' claimed peptide and does not provide the motivation to combine the references to arrive at the claimed invention. Furthermore, Rowland-Jones relates to the production of HIV immunogenic peptides for treating HIV infection. The claimed peptide is a fragment of the Her2/neu polypeptide which is over expressed in many different types of cancer. Thus, Applicants assert that there is no motivation to combine a Her2/neu reference such as Kawashima with Rowland-Jones which is from a different field and relates to the study of HIV and not treating cancer.

Assuming arguendo, one of skill in the art were to combine the teachings of Kawashima and Rowland-Jones, the combination suggests 92 possible peptides[2]. Given this broad genus, one of skill in the art would not have any motivation to pick applicants' claimed peptide. Indeed, there is nothing in Rowland-Jones, or any of the cited references which teaches that the claimed peptide binds with higher affinity to the HLA-A*6802, which is the motivation provided by the Examiner.

Therefore, Applicants assert that there is no motivation to combine the references as suggested by the Examiner. Furthermore, there is no motivation in Kawashima to

[2] Two positions open, each with two possible amino acid choices - V or T and position 2 and V or L at position 9. $2^2 = 4$ possible peptides * 23 Her2/neu peptides disclosed in Kawashima = 92 possible peptides.

choose the peptide KIFGSLAFL and then modify it as suggested by Sydney or Rowland-Jones and then chose the claimed peptides from the genus of possible peptides.

Furthermore, the Rowland-Jones reference teaches that of the 49 predicted peptides which contained the "predicted HLA-A*6802 motif" (V or T at P2 and V or L at P9) tested, only four peptides were positively recognized in a CTL response assay. *See* Figure 3. Thus the chances of predicting a peptide, relying upon the predicted motif as taught by Rowland-Jones, which then actually produces a CTL response is unlikely. Furthermore, of the four positive peptides in Rowland-Jones, only two contained a V at position 2 and a V at position 9, and two did not. Based on the data in Rowland-Jones one of skill in the art had an 8% (4 positive peptides out of 49 tested) chance of producing a peptide which actual elicited a CTL response in the assay described in the reference. Furthermore, there is no indication that the peptides with a V at positions 2 and 9 were any better than the peptides which had T at position 2 and V at position 9 or T at position 2 and L at position 9 according to Rowland-Jones. Indeed, Figure 3 of Rowland-Jones indicates that all four peptides had similar results in a CTL assay. Rowland-Jones provides no reasonable expectation of success to produce the peptide of the claimed invention for use in eliciting an immune response. Thus, even if the KIFGSLAFL peptide in Kawashima had some how been singled out and combined with Rowland-Jones one of skill in the art would not have had a reasonable expectation of success based upon the teaching of Rowland-Jones to chose a V for position 2 and 9 to arrive at the claimed peptide from the peptide of Kawashima that was functional.

Applicants assert that the Examiner has failed to argue a *prima facie* case of obviousness as the Examiner has provided no motivation as to why one of skill in the art

would have chosen the claimed peptide from the broad genus described in the art. Furthermore, Applicants assert that one of skill in the art reading Rowland-Jones would not have concluded that V or T at position 2 and V or L at position 9 is the motif for predicting peptides that bind the HLA-A*6802 allele. Thus, one or ordinary skill in the art would not have had a reasonable expectation of success given the small percentage of peptides which were functional as taught in the Rowland-Jones reference.

The Examiner set forth an alternative rejection of claims 41, 44, 54, 58, 59, 62, 72, 74, and 75 under 35 U.S.C. § 103(a) for allegedly being nonobvious over Lustergarten *et al.*, *Human Immunology* 52:109-118 (1997) (hereinafter "Lustergarten") in view of Rowland-Jones *et al.*, *J. Clinical Invest.* 102:1758-1765 (1998). Specifically the Examiner alleges that "it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the Her2[369] peptide epitope KIFGSLAFL [the same peptide taught by Kawashima in the previous rejection] taught by Lustergarten et al by substituting a V at position 2 and a V at position 9 (i.e., to produce the peptide KVFGSLAFV, SEQ ID NO: 4233 of the instant application and pharmaceutical composition thereof) as taught by Rowland-Jones et al for peptides that bind to the HLA-A2-like supertype allele HLA-A*6802 taught by Rowland-Jones et al." (Paper No. 061004, p.7). Applicants disagree.

The Examiner also alleges that Lustergarten teaches that the consensus motif for peptide binding to HLA-A2.1 is LIMVAT at position 2 and the C-terminal amino acid of the peptide. The Examiner also discusses a 10-mer peptide, p773 taught by Lustergarten, however the Examiner states that "Lustergarten et al do not teach the peptide KVFGSLAFV (SEQ ID NO:4233 of the instant application." (*Id.*)

The claimed invention is directed to the specific peptide of SEQ ID NO:4233, which is nine amino acids in length, and compositions comprising this peptide. Thus, the peptide of Lustergarten which is ten amino acids in length is not obvious in view of the amended claims. Furthermore, Applicants reiterate the argument from above that the Examiner has failed to make a *prime facie* case of obviousness because there is no motivation to combine these two references and no reasonable expectation of success based on the disclosure in Rowland-Jones. Additionally, Lustergarten does not mention the HLA-A*6802 allele, thus there would be no motivation to combine Lustergarten with Rowland-Jones. Thus, Applicants assert that for the reasons previously provided, that the combination of Lustergarten in view of Rowland-Jones fails to establish a prima facie case of obviousness of the peptide and compositions comprising the peptide of the claimed invention.

The Examiner has also rejected claims 42, 43, 45-53, 55-57, 60, 61, 63-71 and 73 under 35 U.S.C. § 103(a) for allegedly being obvious over Kawashima *et al.*, *Human Immunology* 59:1-14 (1998) in view of Sydney *et al. Immunology Today* 17:261-266 (1996) and Rowland-Jones *et al.*, *J. Clinical Invest.* 102:1758-1765 (1998) as applied to claims 41, 44, 54, 58, 59, 62, 72, 74 and 75 and further in view of WO 95/19783 A1 to Kubo *et al.* (Hereinafter "Kubo"). Specifically the Examiner alleges that it would have been *prima facie* obvious to make the peptide of the invention as argued above and that it

> would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to have fused the peptide(s) to a Th peptide such as the universal Th peptide epitope taught by WO 95/19783A1 as taught by WO 95/19785A1 [sic] for other immunogenic CTL epitope peptides, to have fused the peptide(s) to linker amino acid residues and to a carrier or link it to a lipid or to administer it via a liposome, or to make it as a homo or heteropolymer or a composition

> comprising more than one immunogenic peptide as taught by WO 95/19783A1 for other immunogenic peptides.

(Paper No. 061004, p.9). The Examiner further states that one of ordinary skill in the art "would have been motivated to do this in order to make a more effective peptide composition capable of stimulating an immune response, as taught for the fusion peptides, or lipid linked peptides or liposome administered peptides taught by WO 95/19783A1." (*Id.*)

Applicants assert that it would not have been *prima facie* obvious to make the peptide of the invention linked to Th helper peptides, a carrier, a lipid, spacer molecules, administer via a liposome or to make it as a homo or heteropolymer or a composition comprising more than one peptide because, as discussed above, the examiner has not established a *prima facie* case of obviousness of the peptide of the claimed invention over Kawashima in view of Sydney and/or Rowland-Jones. Furthermore, Applicants reiterate the argument from above that the Examiner has failed to make a *prime facie* case of obviousness because there is no motivation to choose any one of the peptides in the broad genus of peptides described in the references to arrive at the claimed peptide, no motivation to combine these two references and no reasonable expectation of success based on the disclosure in Rowland-Jones. Thus, Applicants assert that if the claimed peptide is not obvious that the combination of references cited by the Examiner cannot make the peptide linked to any other molecule obvious.

The Examiner has set forth an alternative rejection of claims 42, 43, 45-53, 55-57, 60, 61, 63-71 and 73 under 35 U.S.C. § 103(a) for allegedly being obvious over Lustergarten *et al.*, *Human Immunology* 52:109-118 (1997) in view of Rowland-Jones *et*

al., J. Clinical Invest. 102:1758-1765 (1998) as applied to claims 41, 44, 54, 58, 59, 62, 72, 74 and 75 and further in view of WO 95/19783 A1 to Kubo *et al.* Specifically the Examiner alleges that it would have been prima facie obvious to make the peptide of the invention as argued above and that it

> would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to have fused the peptide(s) taught by the combination of Lustergarten et al and Rowland-Jones et al to a Th peptide such as the universal Th peptide epitope as taught by WO 95/19783A1 for other immunogenic CTL epitope peptides, to have fused the peptide(s) to linker amino acids and to a carrier or link it to a lipid or to administer it via a liposome, or to make it as a homo or heteropolymer or a composition comprising more than one immunogenic peptide as taught by WO 95/19783A1 for other immunogenic peptides.

(Paper No. 061004, p.11). The Examiner further states that one of ordinary skill in the art "would have been motivated to do this in order to make a more effective peptide composition capable of stimulating an immune response, as taught for the fusion peptides, or lipid linked peptides or liposome administered peptides taught by WO 95/19783A1." (*Id.*)

Applicants assert that it would not have been *prima facie* obvious to make the peptide of the invention linked to Th helper peptides, a carrier, a lipid, spacer molecules, administer via a liposome or to make it as a homo or heteropolymer or a composition comprising more than one peptide because the peptide of the claimed invention is not obvious in light of the arguments set forth above. Furthermore, Applicants reiterate the argument from above that the Examiner has failed to make a *prime facie* case of obviousness because there is no motivation to choose any one of the peptides in the broad genus of peptides described in the references to arrive at the claimed peptide, no

motivation to combine these two references and no reasonable expectation of success based on the disclosure in Rowland-Jones. Thus, Applicants assert that if the claimed peptide is not obvious that the combination of references cited by the Examiner cannot make the peptide linked to any other molecule obvious.

Not acquiescing in the propriety of any of the 103 rejections made by the Examiner, Applicants have cancelled claims 42, 43, 44, 49, 55-57, 59, 60-63, 66-71, 73 and 74. In view of the above arguments, Applicants respectfully request that the Examiner withdraw the rejections of remaining claims 41, 45, 46, 47, 48, 50-53, 54, and 58.

Double Patenting

Claims 41-75 have been provisionally rejected under the doctrine of obviousness-type double patenting over claims 1-10 and 15-27 of copending U.S. Published Application No. 2004/0018971 A1 and claims 1-4, 6-13, 18-31 and 35-38 of copending U.S. Published Application No. 2003/0224036 A1. Applicants respectfully traverse this provisional rejection, but request that the rejection be held in abeyance until such time as the conflicting claims may be patented.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

Date: December 22, 2004

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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Table 2- Examples of Support for Claims

Claim Language	**Support in This Application**	**Support in Priority Appl. No. 60/141,422**
T helper peptide	p. 50, lines 17-19 and 29-32; p. 51, lines 1-2	p. 16, line 19 through p. 17, line 5
Spacer	p. 50, lines 20-27	p. 16, lines 24 through p. 17, line 2
Carrier	p. 42, lines 26-27; p. 43, lines 1-4	p.20, lines 9-12
Lipid	p. 51, line 30 through p. 52, line 11	p. 17, lines 8-16
Fusion protein	p. 53, lines 33-34	p.18, lines 16-17
Liposome	p. 51, line 33 through p. 52, line 3; p. 55 line 33 through p. 56, line 15	p. 17, lines 11-13; p. 23, lines 3-19
Pharmaceutically acceptable carrier	p. 55, lines 27-32	p.22, lines 14-19
Linker amino acids	p. 52, lines 14-19	p. 17, lines 26-29
Homopolymer/heteropolymer	p. 42, lines 26-28	p. 20, lines 3-5
Universal T helper cell epitope	p. 43, lines 22-25 p. 51, lines 12-20	p. 20, lines 30-32
Different peptides	p. 42, lines 28-32	p.20, lines 4-8
8, 9, 10, or 11 amino acids in length	p.12, lines 32-34	p. 5, lines 1-3